REMARKS

Applicant elects Group I, claims 1, 2, and 11-16 drawn to the fusion protein with traverse. Applicant further elects Species A directed to the ligand epidermal growth factor (EGF) family with traverse, and to which the elected claims of Group I are readable on, for example claims 2 and 14-16. Claim 13 is amended to correct its dependency. Claims 17-20 are canceled without prejudice or disclaimer. Claims 21-30 are added and supported in Applicant's original disclosure. No new matter has been added. Claims 1, 2, 11-16, and 21-30 are pending.

Applicant respectfully submits that the pending claims possess unity of invention for at least the following remarks herein. Favorable consideration and examination of the pending claims is respectfully requested.

The Restriction contends that "[T]he inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features," because Kihara and Pastan read on the claim in that Kihara and Pastan teach a chimeric toxin comprised of transforming growth factor α (TGFα) fused to *Pseudomonas* exotoxin (PE) which bind to the epidermal growth factor receptor and kill cells expressing epidermal growth factor receptor. The rejection further contends that, because TGFα is a peptide that directly interacts with a cancer cell surface and PE is a superantigen, claim 1 is not special in view of Kihara and Pastan and the groups are not so linked as to form a single general inventive concept.

Applicant respectfully disagrees, and contends that PE does not satisfy the superantigen feature of claim 1. Kihara and Pastan do not provide any description or suggestion that PE is a superantigen. In fact, Kihara and Pastan provide at page 5154, right column, 1st paragraph that:

PE is a Mr 66,000 protein that contains three structural domains. Domain Ia (amino acids 1-252) is the cell binding domain, domain II (amino acids 253-364) is responsible for translocation into the cytosol, and domain III (amino acids 400-613) catalyzes the ADP-ribosylation and inactivation of elongation factor 2, which inhibits protein synthesis and leads to cell death. During the intoxication process, PE is cleaved by an intracellular protease between amino acids 279 and 280 to generate a Mr 37,000

carboxylterminal fragment that contains the ADP-ribosylation activity.

Furthermore, at page 5154, 2nd paragraph of the right column in the reference mentions a modified PE protein, TP40, which is selectively cytotoxic. However, one of skill in the art would recognize that "cytotoxic" as meant in the reference is different from T-cell cytotoxicity of a superantigen. Superantigens, as described in Applicant's specification are a class of special antigens, which mainly include certain bacterial toxins and retroviral gene products (see for example page 1, paragraph 4). Without processing by antigen presenting cells (APC), superantigens, as intact proteins, bind to and form complexes with MHC Class II molecules on the cellular membrane. They recognize the T cell receptor (TCR) V β chain and activate significantly more T lymphocytes (including CD4+ , CD8+) than conventional antigens do. Furthermore, superantigens also induce the release of a large amount of cytokines and produce effective cytotoxicity on targeted cells.

In view of such descriptions, one of skill in the art would understand that superantigens act in different mechanism of intoxication. That is, superantigens act by stimulating cytokine synthesis and through T cell killing effect. In contract, the PE of Kihara and Pastan inhibits protein synthesis and kill the cells and thus its mechanism is totally different from that of a superantigen. Thus, one of skill in the art would not deem PE as a superantigen. Kihara and Pastan do not disclose or suggest the fusion protein of Claim 1. Accordingly, Applicant respectfully submits that claim 1 possesses a specific technical feature and the claims are linked for at least the foregoing reasons.

Moreover, when cytokines are used in the fusion proteins, the cost of production for antibodies, such as humanizing, massive cell production can be reduced, therefore a new cost efficient and convenient way for cancer treatment and medicine production is provided (see for example page 7, 2nd paragraph of Applicant's specification).

The following references are attached herewith by Applicant as further evidence to clarify the skill level of the skilled artisan:

(1) TGFa-PE fusion protein.

Transforming growth factor a- Pseudomonas exotoxin fusion protein prolongs survival of nude mice bearing tumor xenografts. Proc. Natl. Acad. Sci. USA, 87, 4697-

4701, 1990. D. C. Heimbrook, et al. The reference describes the PE40 action (see page 4697, left column, 2nd paragraph from the bottom). The reference provides no description that PE40 protein is a superantigen or that it induces T-cell cytotoxification.

(2) Treatment of intracranial tumors by systemic transfer of superantigen-activated tumor-draining lymph node T cells. Cancer Res., 56, 4702-4708, 1996. M. Inoue, et al.

In the abstract and introduction part, this reference clearly indicates that superantigens act through T-cell killing of the cancer cells. Furthermore, the activation is not antigen dependent. Therefore, the acting mechanism of superantigens is totally different from PE proteins.

(3) T-cell antigen receptor binding sites for the microbial superantigen staphylococcal enterotoxin A. Proc. Natl. Acad. Sci. USA, 89, 7727-7731, 1992. C. H. Pontzer, et al.

See for example the paragraph below the abstract. SEA has the characteristics of a superantigen because of its ability to stimulate all T cells bearing particular T-cell antigen receptor (TCT) β chain variable regions (Vβ). This reference indicates the characteristic feature of superantigen and proving that PE and superantigens have different action mechanisms.

Moreover, Applicants respectfully submit that the additional references Thomas et al., Holzer et al., Shiah et al., and Dohlsten et al., which are attached herewith, provide further support that PE toxins are not superantigens, and that superantigens act by activating T-cell killing of the cancer, which is a different mechanism than what is exhibited by PE toxins.

Therefore, Applicant respectfully submits that the above evidence supports that PE toxins are not superantigens, and that superantigens act by activating T-cell killing of the cancer, which is a different mechanism than what is exhibited by PE toxins. Accordingly, Applicant respectfully submits that Kihara and Pastan do not disclose or suggest the fusion protein of superantigen and ligands, and that the claims possess unity. The claims are linked and relate to a single general inventive concept under PCT Rule 13.1. Favorable reconsideration is respectfully requested.

Regarding the election of species, the Restriction contends that the species listed do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the species are each receptors from different gene families, having different structures and different functions. Applicants respectfully disagree and submit that the species be examined together as there would not be an undue burden on the Examiner, and at least with respect to the species directed to growth factors. Favorable reconsideration on this issue is respectfully requested.

With regard to added claims 21-30, Applicants respectfully submit that these claims should be examined at least because they read on the elected invention and species. Favorable consideration of these claims is respectfully requested.

In view of the above amendments and remarks, Applicants respectfully request examination of the pending claims, and respectfully request favorable consideration of the claims in the form of a Notice of Allowance. If any questions arise regarding this communication, the Examiner is invited to contact Applicants' representative listed below.

Respectfully submitted,

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